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ORIGINAL RESEARCH

Comparative Results in a Combined Procedure of Intrastromal Corneal Rings Implantation and Cross-linking in Patients with Keratoconus: A Retrospective Study

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ABSTRACT

Introduction: Corneal thinning disorders caused by keratoconus often lead to protrusion, irregular astigmatism, and even perforation. Keratoconus, like other corneal ectasia, does not have a known cause. Severe cases of keratoconus may require correction or restoration of tectonic integrity of the cornea by surgical means. Intracorneal ring segments are a new modality in the treatment of corneal ectactic disorders. A new technique of stopping the evolution of keratoconus and strengthening the cornea is combining techniques of intrastromal corneal ring implantation and corneal collagen cross-linking. The objective of the study is to compare the effectiveness of combined procedures: intrastromal corneal ring implantation followed by cross-linking, with cross-linking followed by intrastromal corneal ring implantation.

Methods: The study comprised two groups of patients with different evolutionary stages of keratoconus, which met the eligibility criteria for intrastromal corneal ring segment implantation and corneal collagen cross-linking. Group 1 included patients (41 eyes) who underwent intrastromal corneal ring implantation followed by cross-linking and group 2 (30 eyes) included patients who underwent cross-linking first followed by intrastromal corneal ring implantation.

Results: A decrease in *Km* values of about 1.5 D and refraction was observed in group 1, compared to a decrease in *Km* values of about 1 D and refraction in group 2. Recovery of visual acuity was higher in group 1 than group 2.

Conclusions: The sequence of intrastromal corneal ring implantation followed by cross-linking proved to be more effective in reducing *Km* values, spherical equivalent and cylinder compared with cross-linking followed by intrastromal corneal ring implantation.

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INTRODUCTION

Keratoconus (KCN) is a progressive degenerative disease of the cornea, usually bilateral, but most of the time asymmetric [1]. In most of the cases, it affects young patients, and an early age of onset is a negative prognostic factor for corneal transplantation [2]. There are several treatment options available, depending on the stage of KCN.

A major breakthrough in blocking the progression of the ectasia is the corneal collagen cross-linking procedure with riboflavin and ultraviolet A (UVA) light [3, 4].

Corneal collagen cross-linking (CXL) means photopolimerisation of the stromal fibrillar tissue in order to increase their stiffness and resistance to the corneal ectasia through the combined action of the photosensitizing substance [riboflavin (vitamin B2)] with UVA irradiation performed with a solid-state UVA illuminator. The final effect of the CXL technique is strengthening of the cornea and the goal of CXL is to slow down or arrest the progression of KCN, avoiding, or at least delaying, the necessity of keratoplasty.

Intrastromal corneal ring segments (ICRSs) are made of polymethylmethacrylate (PMMA) and are a new modality in the treatment of corneal ectactic disorders.

A new technique of stopping the evolution of KCN and strengthening the cornea is combining the two techniques in order to flatten the cornea to correct the irregular astigmatism and improve visual acuity by intrastromal ring implantation and strengthening the cornea through cross-linking.

The purpose of this study is to prove the better of the two procedures for treatment of KCN: intrastromal corneal ring implantation followed by corneal collagen cross-linking, and corneal collagen cross-linking followed by intrastromal corneal ring implantation.

METHODS

We conducted a retrospective study which comprised two groups of patients with different evolutionary stages of progressive KCN. The two groups met the eligibility criteria for intrastromal corneal ring segment implantation and corneal collagen cross-linking.

Group 1 included eyes (41 eyes) that underwent intrastromal corneal ring implantation followed by cross-linking. In this group, we performed ring implantation first, in patients with advanced stages of KCN and high refractive error. After 6 months, we performed CXL.

Group 2 (30 eyes) included patients who underwent cross-linking first followed by intrastromal corneal ring implantation. In this group, we performed CXL first, in patients with early stages of KCN and small refractive error, in which visual acuity could be corrected by glasses or contact lenses. After 6 months, we implanted intrastromal rings to improve visual acuity and lower the astigmatism.

The indication of treatment was made according to the particularity of each case.

The inclusion criteria in each group were based on the refractive error and the stage of KCN.

The inclusion criteria were:

- Patients between 15 and 54 years of age.
- Both genders.
- Diagnosed with progressive KCN—stages 1, 2, 3 and 3/4 according to Amsler Krumeich classification.
- Average thinnest corneal thickness of at least 400 μm.
- Transparent cornea.
- Intolerance of contact lenses.

The exclusion criteria were:

- Patients with an average corneal thickness lower than 400 μm.
- Vogt striae.
- Herpetic keratitis or/and other active ocular infection.
- Patients with severe dry eye disease or aphakia.

The ocular examination included:

- Uncorrected visual acuity (UCVA) and best corrected (BCVA) visual acuity (logMAR chart).
- Ocular refraction and keratometry (Km; TOPCON auto-kerato-refractometer KR 8100P, Japan).
- Slit lamp examination (TOPCON slit lamp, Japan).
- Intraocular pressure measurement (CSO Goldman aplanotonometer, Italy).
- Pachymetry: optic (Oculus Pentacam HR, Germany) and ultrasonic (TOMEY SP2000, Japan).
- Corneal tomography (OCULUS Pentacam HR, Germany).
- Endothelial corneal cell count (TOPCON specular microscope SP 3000P, Japan).

Both techniques were performed in the operating room in sterile conditions.

The intracorneal ring implantation (ICR) technique begins with topical anesthesia followed by application of a sterile operating field and lid speculum. The following steps were: marking the center of the cornea, ultrasonic pachimetry, corneal incision on the steepest meridian with a diamond knife in 80% of the corneal thickness, corneal delamination, performing the intracorneal tunnel (mechanical) and insertion of the intrastromal ring(s) and instillation of antibiotics and steroids. We used both SI-5 and SI-6 kerarings, by Mediphacos Company, Brazil, for implantation in the 5-, 5.5- and 6-mm optical zone, according to the particulars of each case.

For CXL technique a single 3.0 ml, riboflavin 0.1%-to-dextran 20%, solution was opened and the power of the UVA illuminator was checked. The eye was prepped with topical anesthesia (alcaine solution), 3–4 drops, 15–20 min before CXL. A sterile operating field and lid speculum was used. A corneal de-epithelization on a 9-mm diameter was performed. The techniquie included instillation of one drop of alcaine solution, and instillation of riboflavin 0.1% every 3 min for 30 min before irradiation. The central part of the cornea was exposed to UVA light and instillation of riboflavin was performed every 3 min for 30 min, under a power of 9 mW/cm^2. After irradiation, the cornea was washed with balanced salt solution (BSS) solution. At the end of the procedure, topical antibiotics and steroids were applied with a therapeutic contact lens for 3–4 days. The CXL device used was PESCHKE CCL Vario by Swiss-made Company, Switzerland.

Postoperative treatment consisted of topical steroids and artificial tears for 2–3 months. The postoperative check-up was made at 24, 48 and 72 h.

Follow-up was made at 1, 3, 6 and 12 months after the procedures.

Both techniques were performed at 6 months after each other, for both groups.

The statistical analysis was performed with independent "Student's *t* test", a method of decision to help us validate or invalidate a statistical hypothesis with a certain degree of safety. The test could be applied because the value samples [refractometry, keratometry (Km), visual acuity] were independent for each case. We consider the normal value statistically significant (p value < 0.05). We used this test to prove the statistical significance in case of spherical equivalent (SE), cylinder (Cyl) and Km decrease and visual acuity improvement.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

RESULTS

Regarding the gender distribution in our groups, in the first group, the majority were males (59%) and in the second group, the majority were females (60%).

Most patients were 21–40 years old in both groups, 73% in group I and 70% in group II. The most frequent KCN stage was stage II/III in the first group, 22 cases of stages I/II and III, and 9 cases of each stage in the second group (Fig. 1).

The difference between preoperative SE and 12-month SE was 1.68 D in the first group. In the second group, the difference between the two SE values was 1.07 D (Fig. 2a, b). The p value

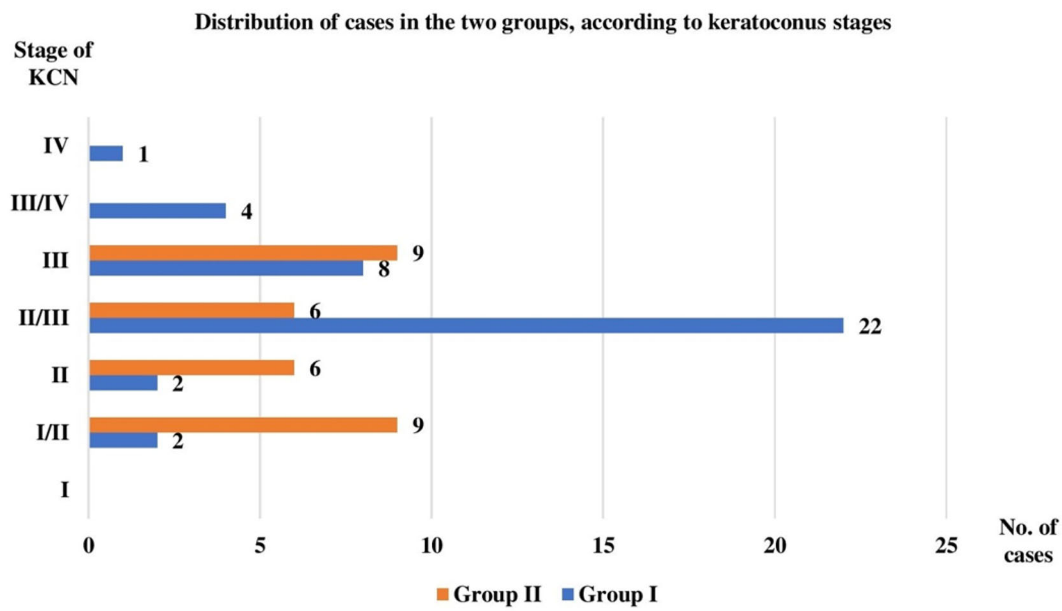

Fig. 1 Stages of keratoconus in the two groups

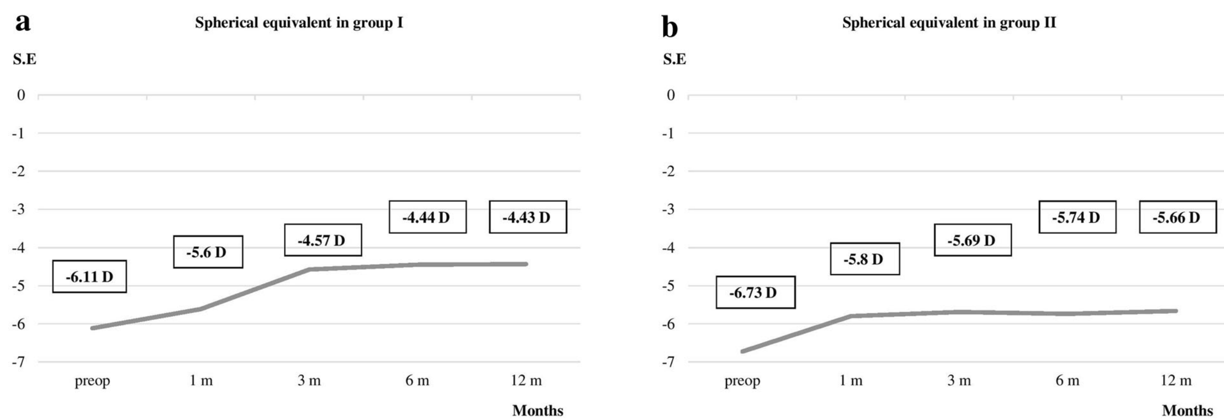

Fig. 2 **a**, **b** Spherical equivalent in the two groups

was statistically significant at 1 month in both groups (Table 1).

The difference between preoperative Cyl and 12-month Cyl was 1.11 D in the first group. In the second group, the difference between the two Cyl values was 0.91 D (Fig. 3a, b). The *p* value was statistically significant at 3 months in the first group and at 6 months in the second group (Table 2).

The difference between preoperative Km and 12-month Km was 2.4 D in the first group. In the second group, the difference between the two Km values was 1.2 D (Fig. 4a, b). The *p* value was statistically significant at 6 months in both groups (Table 3).

Regarding the uncorrected visual acuity (UCVA), the *p* value at 12 months in the first group was statistically significant ($p = 0.00001$), as in the second group ($p = 0.0056$). As we can see, the *p* value is more significant in the first group (Fig. 5a, b).

Table 1 Spherical equivalent p values in the two study groups

Months	p value in group I	Spherical equivalent decrease	Months	p value in group II	Spherical equivalent decrease
1	0.00955	0.51 D	1	0.0498	0.93 D
3	0.004577	1.54 D	3	0.0298	1.04 D
6	0.00004229	1.67 D	6	0.0187	0.99 D
12	0.0000310878	1.68 D	12	0.00987	1.07 D

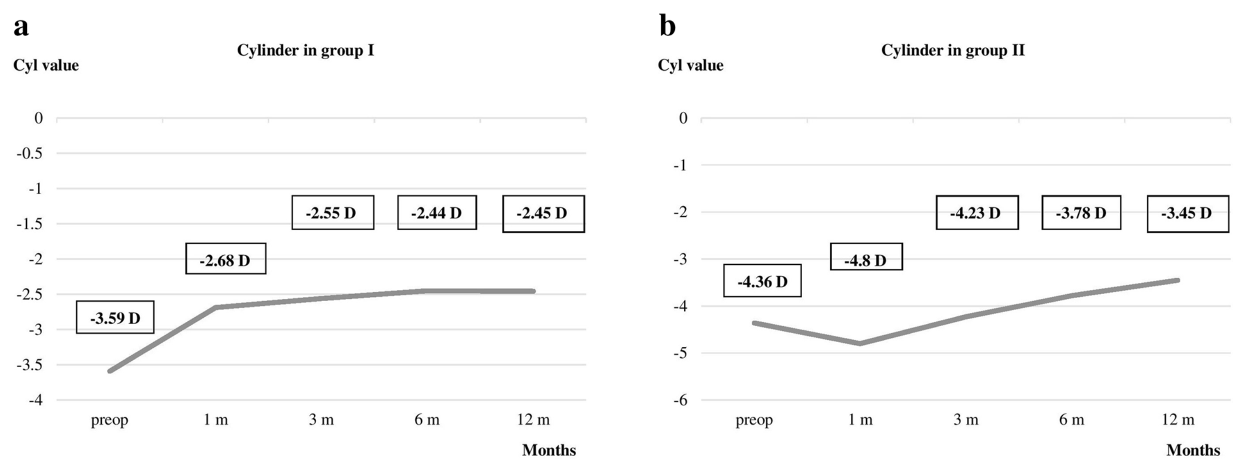

Fig. 3 **a**, **b** Cylinder in the two groups

Table 2 Cylinder p values in the two study groups

Months	p value in group I	Cylinder decrease	Months	p value in group II	Cylinder decrease
1	0.112	0.91 D	1	0.655	− 0.44 D
3	0.005	1.04 D	3	0.067	0.13 D
6	0.000015576	1.15 D	6	0.007645	0.58 D
12	0.0000179238	1.14 D	12	0.003654	0.91 D

In the first group, the majority of patients gained 2 Snellen lines of UCVA (Fig. 6a, b), representing 11 cases, and in the second group, the patients gained 0 and 1 Snellen lines of UCVA (Fig. 8a, b).

Regarding the best corrected visual acuity (BCVA), the p value at 12 months in the first group was statistically significant ($p = 0.00001$), as in the second group ($p = 0.0002$). As we can see, the p value is more significant in the first group (Fig. 7a, b).

In the first group, the majority, 14 cases, gained 4 Snellen lines of BCVA and in the second group, they gained 2 and 4 Snellen lines of BCVA (Fig. 8a, b).

DISCUSSION

Intracorneal rings and the CXL technique have two different primary goals [5]:

– The goal for intracorneal rings is to support the cornea with the ring segments in order

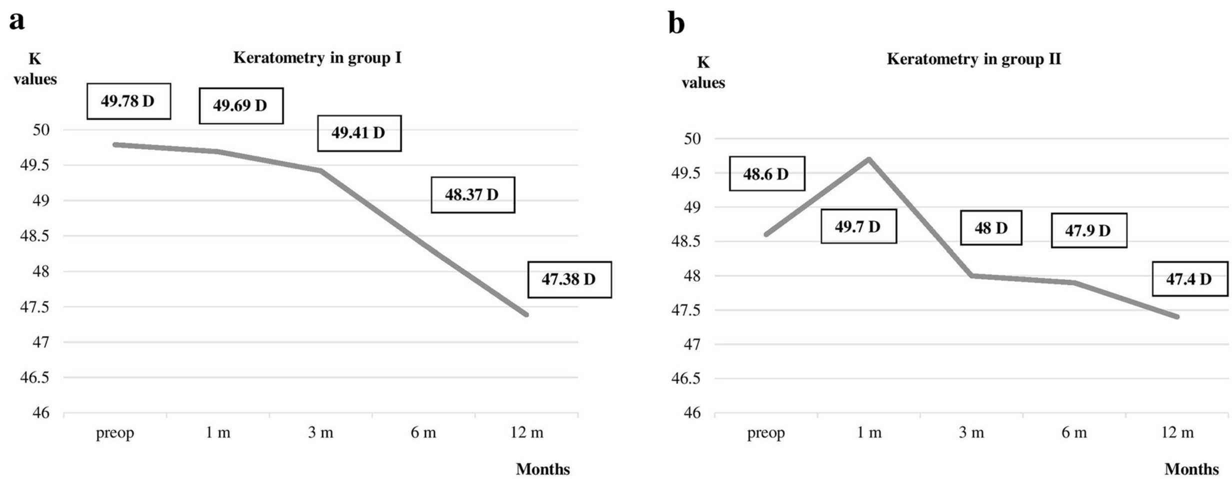

Fig. 4 **a**, **b** Keratometry in the two groups

Table 3 Keratometry *p* values in the two study groups

Months	*p* value in group I	Keratometry decrease	Months	*p* value in group II	Keratometry decrease
1	0.478	0.09 D	1	0.543	− 1.1 D
3	0.114	0.37 D	3	0.498	0.6 D
6	0.045	1.41 D	6	0.0048	0.7 D
12	0.003	2.4 D	12	0.017	1.2 D

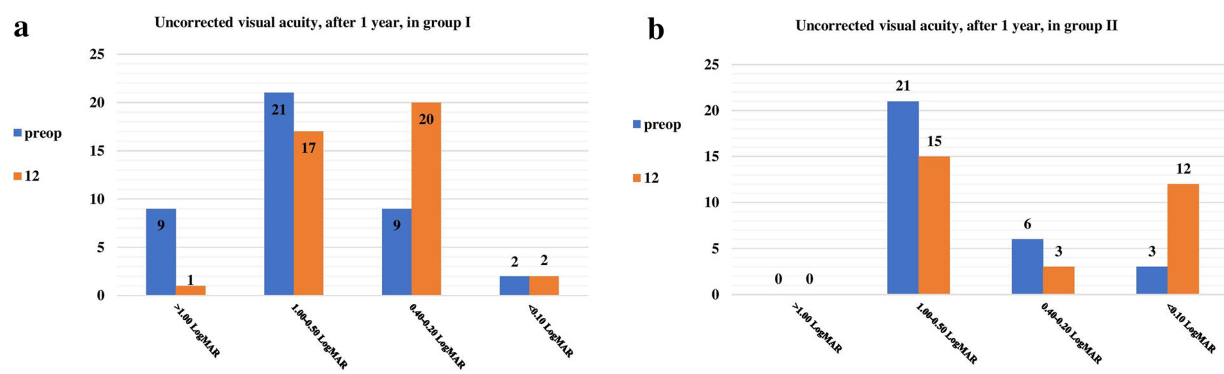

Fig. 5 **a**, **b** Uncorrected visual acuity, after 1 year, in the two groups

to both flatten the cone and to make the corneal contour more symmetric in order to improve contact lens fitting.

- The goal for the CXL technique is to strengthen the cornea in order to prevent progression of the disease over time.
- So, it is better to combine the two procedures together in order to achieve both goals.

The main question remains with which procedure to start.

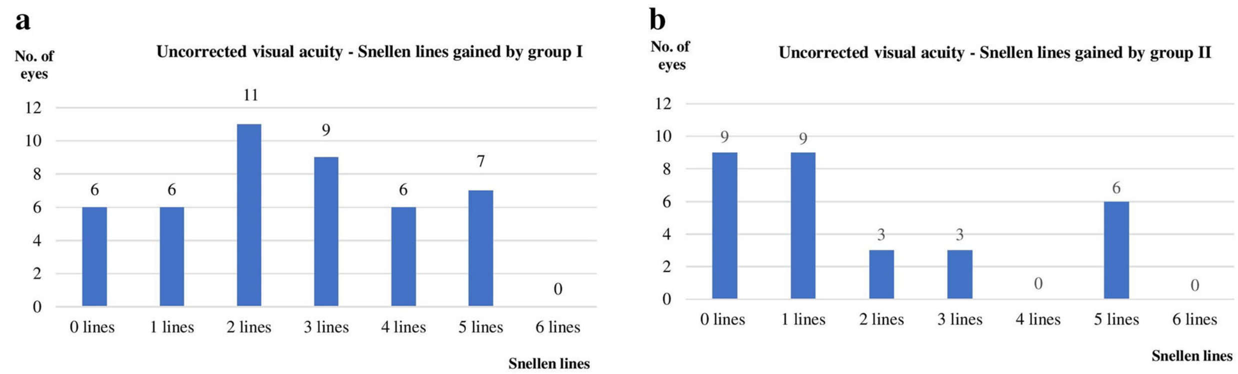

Fig. 6 **a**, **b** Uncorrected visual acuity Snellen lines gained in the two groups

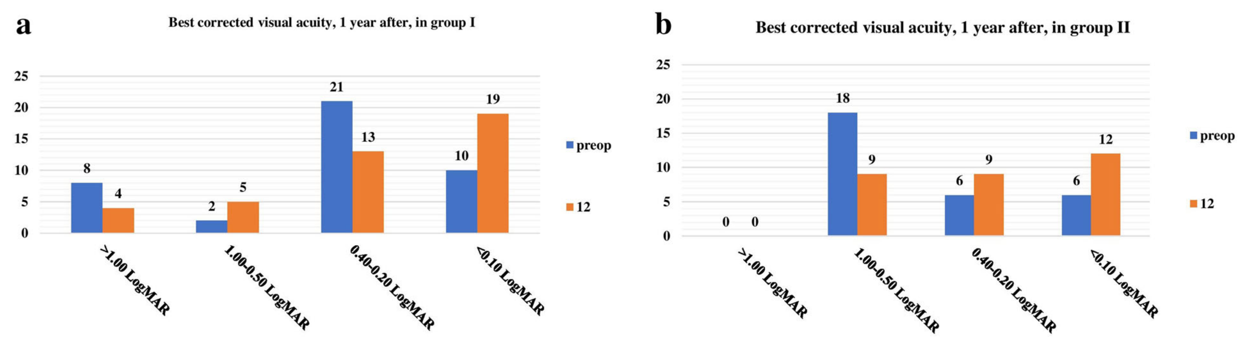

Fig. 7 **a**, **b** Best corrected visual acuity, after 1 year, in the two groups

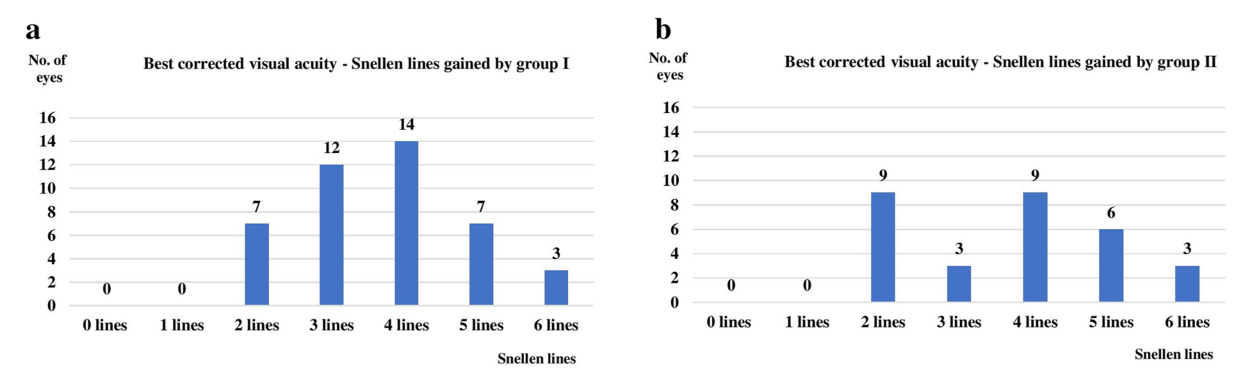

Fig. 8 **a**, **b** Best corrected visual acuity Snellen lines gained in the two groups

In our study, we first performed the CXL technique in young patients with keratoconic progression, and as an initial ICR procedure in patients with contact lens fitting problems and progressive KCN.

Some studies show the beneficial effect of both procedures on the keratoconic eyes and with no statistically significant differences in corneal flattening between the group of patients who first had ICR followed by CXL, and the group of patients who first had CXL and then

ICR implantation. Another conclusion was that keratoconic progression between the two groups showed no differences [5].

Brian Boxer Wacheler reported that there is a statistically greater reduction in Cyl and *Km* values in the Intacs with the CXL group, compared with the Intacs-only group [6].

The increased effect in addition of CXL is caused by two facts: both procedures cause corneal flattening and the channel created for intra-corneal ring insertion may result in localized pooling and concentration of the riboflavin around the ring segment [7–9]. In our study we performed the corneal tunnels mechanically. In the present, the femtosecond laser is also used in order to create the corneal tunnels.

A study conducted in Turkey concluded that intra-corneal riboflavin injection into the tunnel was safe and may provide more penetration without epithelial removal [10].

Corneal collagen change after CXL increased overall biomechanical rigidity by 4.5 times, and the placement of Ferrara rings may modify the pattern and distribution of collagen changes for an enhanced effect [11, 15, 16].

New collagen formation was observed around the Intacs formation. The new fibers may become thicker over time as CXL leads to collagen fiber thickening [12–14] that may contribute to a greater contracture and "pulling back" of the conus [17–19].

Regarding which procedure should be the first, for mild KCN, especially if the patient is young, the first choice has to be CXL. If the patient is middle aged and has a moderate stage of KCN, the first procedure to be done is ICR implantation.

A recent Canadian study found that the combination of ICR placement followed by sequential same-day photorefractive keratectomy (PRK) and CXL may be a reasonable option for improving visual acuity in patients with KCN [20].

The limitations of the current study are the fact that the corneal tunnel was made mechanically (manually), not by a femtosecond laser. If we would have had the possibility of utilizing a femtosecond laser we possibly could have performed both procedures in the same surgical session not at 6 months apart. The predictability in time depends on the stability and position of the rings, and with a femtosecond laser the positioning of the ring at the right depth and axis is better.

CONCLUSIONS

The sequence of intrastromal corneal ring implantation followed by cross-linking proved to be more effective in reducing *Km* values, SE and Cyl compared with cross-linking followed by intrastromal corneal ring implantation.

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Disclosures Cristina Nicula, Radu Nicolae Pop and Dorin V. Nicula have nothing to disclose.

Compliance with Ethics Guidelines All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

Data Availability The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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